protein <0.5 mg/dl), the occurrence of MI remained greater among those with an elevated fibrinogen level (defined as creatine kinase-myocardial band >3 times upper limit of normal: 16.2 vs. 1.0%; p = 0.002; defined as troponin I/T >3 times upper limit of normal: 27.8% vs. 9.2%, p = 0.007). Longer term follow-up reveals that the association between elevated fibrinogen level and occurrence of 6-month MACE after PCI persists independently of on-clopidogrel PI or DM (5).

Identifying impaired metabolism of the clopidogrel prodrug provides an important mechanistic insight for reduced PI in diabetic patients. Further increased on-clopidogrel platelet reactivity correlates with diabetes and higher coronary atherosclerotic disease burden and calcification as detected by angiography or intravascular ultrasound (IVUS) imaging. However, the relationship between coronary artery calcification and body morphology is more complex, with an inverse association reported based on a comprehensive 3-dimensional IVUS-based evaluation. This is of relevance in diabetic patients who usually have a higher body mass index. Nevertheless, elevated serum fibrinogen might be an important mechanistic and clinical link between the presence of impaired on-clopidogrel PI, DM with or without systemic inflammation, and the occurrence of MACE after PCI, especially in patients with a high atherosclerotic disease burden and greater substrate for atherothrombotic events. Although MACE in patients with CAD are attributable to multiple factors, additional studies are warranted to evaluate the role of fibrinogen as an independent biomarker, in the absence of systemic inflammation, of long-term outcomes in patients treated with dual-antiplatelet therapy.

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REPLY: Elevated Serum Fibrinogen

An Independent Link Between Diabetes Mellitus, Impaired On-Clopidogrel Platelet Inhibition, and Major Adverse Cardiac Events After Percutaneous Coronary Intervention

We greatly appreciate the positive comments by Drs. Ang and Mahmud regarding our recent paper, which provided mechanistic insights into the impaired response to clopidogrel in patients with diabetes mellitus (DM) (1). Drs. Ang and Mahmud correctly point out another key mechanism that may be associated with adverse outcomes in patients with DM undergoing percutaneous coronary intervention, which is that associated with elevated serum fibrinogen levels (2,3). Indeed, the investigators have pioneered this field of research that has provided important insights into the complex pathophysiological mechanisms involved in atherothrombotic complications in DM patients. Accordingly, in our paper, we acknowledge that multiple factors, including fibrinogen, are involved in adverse outcomes in DM patients (1,4). However, defining the relative contribution of each of these factors, which may also be patient specific, remains a challenge and indeed beyond the scope of mechanistic studies designed to address a specific hypothesis. The goal of our investigation was to delineate mechanisms involved in the impaired clopidogrel response by integrating quite complex in vitro and ex vivo experiments in the setting of a prospective study including pharmacokinetic and pharmacodynamic assessments (1). Preliminary work by our group and by others have set the foundation for the study design that we used (4,5). We showed that the impaired platelet inhibitor effects of clopidogrel in DM patients is largely attributable to attenuation of clopidogrel's pharmacokinetic profile, characterized by lower plasma levels of its active metabolite and only modestly attributed to altered functional status of the $P2Y_{12}$ signaling pathway (1). Indeed, this mechanistic study is simply 1 piece of a puzzle of an overall very complex disease status in DM patients. Although other factors were not addressed, this does not exclude their important role. Moreover, the observation that not all DM patients with impaired response to clopidogrel or

even elevated levels of fibrinogen have atherothrombotic recurrences further underscores the need for larger studies aimed at best defining factors associated with adverse outcomes. This will set the foundation for dedicated studies not only assessing the mechanistic role of each of these factors but also help define the interplay among them.

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Is CABG Superior to DES for Repeat Revascularization in Patients With Isolated Proximal LAD Disease?

We read with great interest the paper by Hannan et al. (1) comparing the clinical outcomes in a large number of patients with isolated proximal left anterior descending (PLAD) coronary artery disease who underwent coronary artery bypass graft (CABG) surgery and percutaneous coronary interventions (PCIs) with drug-eluting stents (DES). They showed that there were no statistically significant differences in mortality or mortality, myocardial infarction (MI), and/or stroke between the CABG and PCI-DES groups, whereas CABG patients had significantly lower repeat revascularization rates.

Despite the important findings of the study, there are some concerns for the clinical application of these results. First, the type of DES used in the PCI-DES group was not clarified. New-generation DES have been proved more effective and safer than first-generation drug-eluting or bare metal stents (2). Considering this superiority of second-generation DES, it would be appropriate for study results to be adjusted for stent type/stent generation (3).

A study by our group compared the outcomes in patients with isolated PLAD coronary artery disease who underwent CABG and PCI with first-generation DES (4). This study showed that there were no statistically significant differences in major adverse cardiac events (MACE), all-cause mortality, cardiac death, myocardial infarction, and target vessel revascularization between the 2 groups.

Another issue that emerges from the paper is the definition of the endpoints. The use of all-cause mortality but not cardiac death and stroke or MI in the complex index of MI/mortality/stroke in the unmatched patients and propensity-matched patients analysis may differentiate the final results. Indeed, in the analysis of patients without a previous MI, when the authors add MI and stroke to the all-cause mortality, the complex index tends to be statistically significant in favor of CABG (adjusted hazard ratio: 0.96; 95% confidence interval: 0.86 to 1.06). A table showing the adjusted hazard ratios for MI, cardiac death, and stroke separately is needed (5).

The comparison of CABG and PCI-DES in patients with PLAD coronary disease still remains a controversial issue, especially with second-generation DES for which further investigation is needed. Until then, updated guidelines of scientific associations and clinicians' medical criteria define the appropriateness of the method followed.

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